THE PHYSIOLOGICAL ACTION OF THEBAIN.

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THE alkaloids of opium as far as discovered at present are as follows: morphia, narcotina, codeia, thebain, narcein, pseudomorphia, papaverina, cryptopia, opianin, metamorphia, codamin, hydrocotarnia, lanthopin, laudanin, laudanosia, meconidin, and protopin. There are seventeen alkaloids and two organic acids. Apomorphia and codamin are derivatives, the first of morphia, the second of narcotin.

Thebain, or paramorphia, was discovered by Pelletier and Thiboumery in 1832. Couërbe obtained from forty pounds (livre) of opium fifty ounces of morphia, one and a half ounces of codein, one ounce of thebain, one ounce of meconin, and six drachms of narcein. Merck found in Bengal opium eight per cent. of morphia, three per cent. of narcotin, one per cent. of thebain, one half per cent. of codein, and a trace of meconin.

Magendie[1] first made physiological experiments with thebain. He found that one grain (probably the acetate), injected into the jugular or into the pleura, tetanized and killed dogs.

Orfila experimented with the nitrate (?) of thebain on dogs. In the first experiment ten centigrammes of the salt with twelve grammes of water were introduced into the jugular of a dog having fasted a long time. The animal soon made a deep inspiration, and fell into opisthotonos with convulsive movements, which lasted a few seconds. After a minute the walk of the dog was vacillating, as though he was intoxicated, but no paralysis of the posterior extremities was perceived. Drowsiness was also present. After ten minutes the animal began to recover, and next day was quite lively. In the second experiment Orfila injected into the jugular vein of a moderately strong dog a solution of thirty-five centigrammes of nitrate (?) of thebain in twenty grammes of water. Before the end of the injection, opisthotonos and convulsive movements ensued. After many curious movements the animal recovered in about twenty minutes.

Albers made two experiments on frogs, with thebain in crystallized

[1] Das Thebain: Eine Monographie. F. W. Müller, Marburg. 1868.

form. He gave one half and three fourths of a grain subcutaneously. The toxic action appeared slowly. Convulsive cramps were observed, and death took place after a considerable time. Müller thinks that Albers used another alkaloid, probably caffein, but I see no very good reason to doubt Albers's observations.

Bernard experimented on dogs, cats, rabbits, guinea-pigs, rats, pigeons, sparrows, and frogs. He found thebain the quickest convulsivant, and, other things being equal, the most deadly toxicant, compared with the five alkaloids, codein, morphia, narcein, narcotin, and papaverin. He states that a dog of seven to eight kilogrammes in weight died when one tenth of a gramme of thebain in the shape of a muriate was injected into the blood. He further states that thebain caused not only convulsions but stoppage of the heart, and quickly ensuing rigor mortis.

Baxt[1] made a difference between large and small doses as regards effects on frogs. By the subcutaneous injection of about .00075 of a gramme of thebain dissolved with hydrochloric acid and water, there ensued at first excitation for a minute, followed by rest; in three to six minutes a comatose state, in which only strong irritation brought out a single reflex contraction, and after twelve to eighteen minutes a state similar to that induced by strychnia — spontaneous cramps, and a heightened excitability lasting from three to six hours. These appearances could be brought out when the dose was repeated on the same day or on successive days. Frogs which had received .00225 of a gramme and .0045 of a gramme subcutaneously, had reflex tetanus at first, which became spontaneous, and the animals died in from two to six hours. When six or seven thousandths of a gramme were introduced subcutaneously in rabbits, in fifteen to twenty-five minutes strong tetanus was produced, usually ending in death. The same dose caused strong excitation in guinea-pigs. In frogs thebain contracted the pupil, then enlarged it, and after one to two hours contracted it considerably. It increased the frequency of the heart-beats.

Müller used the muriate of thebain in watery solution on frogs, pigeons, rabbits, and dogs. In a medium-sized dog, one tenth of a gramme under the skin was not deadly, but it became so after a period of seventeen minutes when injected into the jugular vein. The subcutaneous injection of .005 of a gramme subcutaneously in rabbits had no effect, but when received into the jugular, tetanus ensued but not death. Doses varying from one tenth of a gramme to two grammes, subcutaneously, produced death in three experiments on rabbits in twenty-one, eight, and six minutes. Four hundredths of a gramme of thebain produced in a pigeon tetanic cramps at the end of six minutes, whilst five hundredths and one tenth of a gramme produced death in

[1] Husemann, Die Pflanzenstoffe.

different pigeons at the end of four, seven, and eleven minutes. Müller concludes that, other things being equal, pigeons have a greater resistance to the poison than rabbits. He saw very small quantities of it produce tetanus in frogs, and stand-still of heart. When excised frogs' hearts are placed in a weak solution of thebain and in distilled water, the beats of the hearts in the thebain solution decrease in number more rapidly, and cease earlier. Müller infers that morphia and thebain are not antagonistic in action. Crum Brown, and Fraser saw twelve thousandths of a gramme of thebain, dissolved in very dilute hydrochloric acid and introduced subcutaneously, kill a rabbit in forty-four minutes, the symptoms previous to death being absence of a desire to move, contractions of the muscles about the spine, and opisthotonos; twenty-four hundredths of a gramme in the same form, when given by the stomach, caused tetanus and death in nineteen minutes. Rigor mortis and acid reaction of the muscle appeared, and the sciatic nerves were irritable fifteen minutes after death. Harley has seen a dog die when two grains were used hypodermically, and mice succumb from the use of one half to one twentieth of a grain. Mitchell[1] found that a grain of paramorphia (Powers and Weightmann's article), partially dissolved, caused death in a pigeon, in two minutes, attended with tetanus, and that one third of a grain dissolved in thirty minims of acidulated water produced death, accompanied by vomiting and tetanus, in one minute and a half. Rabuteau[2] injected subcutaneously, in a dog, five centigrammes of thebain dissolved by a drop of muriatic acid, and the only symptom was stamping on the ground with the feet. In another dog, fifteen to twenty centigrammes dissolved in five cubic centimetres of water, given in the same way, caused symptoms similar to those by strychnia, followed by death. The pupils were slightly contracted. Rabuteau also saw thebain in small doses cause convulsions and death in frogs. He has taken, at one time five centigrammes, and at another time ten centigrammes of thebain, dissolved in hydrochloric acid, with subsequent ingestion of a hundred grammes of water. After the dose of ten centigrammes, the only symptom was some cerebral trouble, such as ebriety without headache; there was no action on the pupil, pulse, appetite, or urinary secretion.

Ozanam[3] states that thebain therapeutically agitates and even tetanizes, with slight predisposition to sleeplessness; it excites tetanus principally in the upper limbs (a fact noticed by Orfila in a dog), suggesting that it may be beneficial in paralysis of those parts. Three to six centigrammes in a paraplegic patient caused so much general uneasiness and

[1] American Journal of the Medical Sciences, January, 1870.
[2] Journal de l'Anatomie et de la Physiologie, No. 3, 1872.
[3] G. B. Wood's Therapeutics.

excitation, especially of the upper extremities, that the remedy was discontinued. Schroff thinks that therapeutically thebain is worthless. Reissner saw no narcotic symptoms from it. The observations of Eulenberg coincide with those of Ozanam that it acts especially on the cervicodorsal part of the spine. He found that the subcutaneous use of the muriate of thebain in doses of twelve thousandths to four hundredths of a gramme, by several patients, increased the temperature and the number of pulsations and respirations with no symptoms of intoxication. In a few cases wide dilatation of the pupil was noticed. The drug had neither hypnotic nor analgesic effect, nor action on diarrhœa. Rabuteau, by the method of Moreau, found that thebain does not prevent exosmosis. He concludes that thebain is convulsivant and toxicant, not soporific, but increases the action of chloroform and is analgesic.

Having given a general *résumé* of the knowledge on this subject, I will relate my own experiences. All my experiments were made with Merck's thebain. One cubic centimetre of the solution equaled one hundredth of a gramme of the poison dissolved by hydrochloric acid, the solution being absolutely neutral. As it will be inconvenient to present a complete tabular statement of experiments, I will give only enough to illustrate my statements.

GENERAL ACTION.

Experiment I. — Frog at 1.23 P. M. received .01 gramme of thebain subcutaneously. At first frog hops away, then sits still; pupil contracted, respiration less frequent. 1.29 P. M. Tetanus excited by touch; medulla severed, but tetanus persists till death at 2.10 P. M.; heart beats eighteen per minute..

Experiment II. — Frog at 9.32 A. M. received .00075 gramme of thebain subcutaneously. At first hops away, then remains quiet. 9.37 A. M. Pupils become smaller. 10.56 A. M. Tetanus, which continued during the afternoon; at length fully recovered.

Experiment III. — A pigeon of moderate size received under the skin of the thigh .01 gramme of thebain at 2.45 P. M. At first the bird flew about the laboratory, then showed signs of excitation. 2.52 P. M. Fell from his perch in a tetanic state, which continued at frequent intervals till 2.58 P. M., when death ensued. When the chest was opened, the heart was not beating.

From the above experiments it is seen that thebain is a tetanizing agent, even in as small doses as .00075 of a gramme; that the seat of the convulsions is not cerebral; that pigeons do not have a special immunity against it, as was demonstrated by Mitchell[1] in the case of morphia.

[1] American Journal of the Medical Sciences, January, 1870. Opium and its Derivative Alkaloids.

ACTION ON THE NERVOUS AND MUSCULAR SYSTEMS.

In all cases of poisoning by thebain the functions of the sensory nerves remain unimpaired till death, as the convulsions are always excited by touch up to that period. In studying the action on the sensory nerves I made use of the method described by Von Bezold and Bloebaum.[1] In a few words the method is as follows. The reflex contractions of a frog, feebly under the influence of strychnia, afforded an index of sensory excitation, as used by Pflüger.[2] The main arteries of the hind legs were previously tied, and these extremities so severed that their only connection with the body was by the sciatic nerves. One nerve was covered with cotton saturated with two and a half per cent. solution of phosphate of soda, and to the other a two and a half per cent. solution of muriate of thebain was applied in the same manner. Two watch-glasses were the sources from which the cotton received sufficient solution to be always thoroughly saturated. By means of a support and a rubber ring four pairs of platinum electrodes were adjusted in such a way that by means of commutators the central or the peripheral parts of the nerves, *i. e.*, the parts above and below the points of application of the drugs, could be irritated separately at will. In all details the method as fully described in places referred to was followed; the results of this method can be judged of only in a general way, as the physical laws of the osmosis of the poisons are not made out as regards the nerves.

S. C. means the central end and S. P. the peripheral end of the nerve soaking in the soda solution. T. C. means the central end and T. P. the peripheral end of the nerve saturated with the thebain solution. The numbers under these letters denote the distance between the primary and secondary coils at which the central or the peripheral part of the nerve is sufficiently irritated to respond by a reflex contraction.

Experiment I.

Time.	S. C.	S. P.	T. C.	T. P.
A. M. 11 5	27	27	25	21
11 10	28	28	20	27
11 30	24	28	22	20
11 40	25	24	13	15
P. M. 1 35	15	10	12	12
2 12	17	11	11	11

From the figures in the above table it will be seen that the nerve to which thebain was applied was in general less irritable than that treated

[1] Von Bezold, Untersuch. aus dem physiologischen Laboratorium in Würzburg, erstes Heft, page 21.

[2] Untersuch. aus dem physiologischen Laboratorium zu Bonn.

with phosphate of soda, but, owing to the irregularities shown in the last two columns, it would be unsafe to attribute this diminished irritability to a specific action of the drug upon the sensory nerve trunks. I have also made use of the beautiful method of Brown-Séquard [1] by cutting off the action of the poison on the lower segment of the spine and sending it to the peripheral terminations of the nerves going to this segment.

Experiment II. — Frog has cord cut at origin of nerves of anterior extremities and the spinal branches of the aorta severed. Then .0025 of a gramme of thebain was injected under the skin of the lower jaw at 10.45 A. M. At 10.52 A. M., tetanus of the anterior extremities occurred; posterior extremities are withdrawn when pinched. 11.22 A. M. No tetanus of posterior extremities, although anterior extremities are tetanized.

In the following experiment the poison is cut off from the peripheral ends of the nerves of the posterior extremities, but is allowed to go to the spinal cord.

Experiment III. — Frog at 10.28 A. M. had aorta tied above its bifurcation, and .0025 of a gramme of thebain injected under the skin of the lower jaw. 10.31 A. M. Tetanus in all extremities; no distinguishable preference shown.

The following experiment shows the local action of thebain when applied to the spinal cord.

Experiment IV. — Frog has cord cut at the origin of the brachial plexus, and spinal arteries of aorta severed; .0025 of a gramme of thebain was gently injected into the spinal canal of the lower segment, when tetanus ensued, lasting a minute and a half, after which all reflex action in posterior extremities was lost.

The action of the poison on the peripheral end of the sciatic nerve on one side can also be studied by the method of Bernard, as is shown in the following experiment.

Experiment V. — Frog has right iliac artery and vein tied. At 9.7 A. M. he received .015 of a gramme of thebain. 9.11 A. M. Tetanus. 9.12 A. M. Again .015 of a gramme injected; pupil contracted. 10.4 A. M. No sign of life. Sciatic nerve on sound side responds at fifty centimetres of Dubois's coil, sciatic nerve on poisoned side responds at forty-five centimetres; no reflex action on irritating either central end of the sciatics; thrusting an instrument down the spine elicits a few very slight twitches in the femoral muscles.

It is evident from the above experiments that the action of the poison on the sensory and motor nerves is nothing at all. Now the question arises, Where is the seat of the tetanus? It has already been proved

[1] Thèse pour le Doctorat en Médecine par F. W. Bonnefin.

that it is non-cerebral. As for every reflex action we must have a sensory nerve, a ganglion, a motor nerve, and a muscle, the seat of this tetanus must be in either one or more of the above elements. The method of Brown-Séquard shows that the action of the poison on the sensory termination will not produce tetanus, and Experiment V. proves that the excitability of the motor nerves certainly is not exaggerated by it; so that it is necessary to conclude that the action must be either in the ganglion or the muscles. But there is no action on the muscles, for as division of the sciatic stops convulsive action in that extremity, and repeated observations of muscle curve gave me wholly negative results. The action of the muscle was studied by means of Pflüger's myograph. I first severed the medulla, destroyed the spinal cord, and took a curve of the gastrocnemius indirectly and directly in situ. Then the frog was poisoned by subcutaneous injection of thebain, and curves of same muscle taken at different periods for an hour or two. All curves were registered on Ludwig's registering apparatus.

The following form will express my conclusions as to the action of thebain on the nervous system: —

1. Thebain is a spinal convulsivant.
2. It has no action either on the sensory nerves, the striated muscles, or the motor nerves.
3. Like strychnia, it tetanizes by excitation of the spinal ganglia.

ACTION ON THE CIRCULATION.

The experiments on the circulation were twenty-six in number, and were made on rabbits. The pulse and pressure were noted by Ludwig's mercurial manometer on a continuous roll of paper, whose rapidity of movement was noted by an electro-magnet in connection with a pendulum swinging seconds. By a special contrivance the beginning and end of the injection were noted on the paper. A branch of the jugular or the jugular itself furnished the means for the introduction of the poison, which was always injected towards the heart, no air being allowed to enter. Artificial respiration, similar to the normal, was kept up by an apparatus on the principle of Sprengel's blower, the current being broken at regular intervals by a revolving stop-cock. Curare was used to prevent the effect of the tetanus on the circulation. The carotid artery was used for manometrical observations. The pressure of the blood is given in millimetres of mercury, and the pulsations for periods of thirty seconds.

Experiment I. — Rabbit, curarized.

Time.	Pulse.	Pressure.
	134	96
	Thebain, .005 gramme.	
P. M. 1 20	142	134
1 20 30	138	126
1 21	140	118
1 22	135	144
1 30	118	140
1 48	120	100
2 10 30	108	98
	Thebain, .005 gramme.	
2 11 15	107	74–108
2 11 45	35	72
2 12 15	50	92
2 12 45	85	122
2 13 15	91	122
2 40 45	83	84

Experiment II. — Rabbit, curarized.

Time.	Pulse.	Pressure.
	147	90
	Thebain, .0025 gramme.	
A. M. 9 1	146	86–106
9 1 30	139	104
9 2	150	100
9 3 30	143	112
9 5	148	112
9 7 30	139	114
9 12 30	125	106
9 18	121	94
9 24 30	127	118
10 19 30	99	94
	Thebain, .005 gramme.	
10 19 45	97	90–118
10 20 15	35	148
10 21 15	64	162
10 21 45	77	162

Experiment III. — Rabbit, curarized.

Time.	Pulse.	Pressure.
	98	78
	Thebain, .0025 gramme.	
P. M. 12 30 30	104	78
12 31	135	105
12 31 30	154	126
12 32	111	110
12 32 30	104	112
12 33 30	115	129
12 34 30	83	89
12 38 15	104	96
12 41	94	80
	Thebain, .0025 gramme.	
12 41 45	113	105
12 42 15	118	138
12 43 45	99	132
12 52 45	96	72
12 53	Thebain, .0025 gramme.	Rabbit dead.

It will be seen by the above experiments that thebain increases the blood-pressure and pulse, there being in some cases a temporary fall of pressure for a few seconds, immediately after the injection, probably due to contact of a foreign substance. If, now, the heart and vascular system with nerves intact give such a result, the next question will be what nervous apparatus is involved in their production. Recent researches in physiology have demonstrated that the circulation is influenced by at least four different nervous apparatuses.

1. Ganglia imbedded in the heart, which cause the rhythmical contractions of the heart, called excito-motor ganglia.

2. Nerves in the cardiac branch of the pneumogastrics which arise from a reflex centre in the medulla and end in the cardio-inhibitory ganglia situated in the heart; their action is to slow the heart.

3. The accelerator nerves, or excito-cardio-motor apparatus, which increase the heart-beat. These nerves are not in constant action.

4. The vaso-motor centre (recently located by Owsjannikow and Dittmar) whose nerves, running to the muscular fibres situated in the vascular walls, regulate the calibre of the vessels, and thus increase or diminish the pressure.

Now the frequency of the pulse can be increased by increase of temperature, through direct action of thebain on the excito-motor ganglia located in the heart, through irritation of the accelerator nerves, and through paralysis of the pneumogastrics. The increase of the pulse by the increased pressure is still *sub judice*. The temperature during the experiments was falling instead of rising, which excludes the first of the above-mentioned possibilities.

ACTION OF THEBAIN ON CARDIO-INHIBITORY APPARATUS.

There are several methods of studying this action. One is to poison the animal, and to sever the pneumogastrics when it is completely under the influence of the poison; or to sever the vagi first, then poison, and compare the effects with those obtained with the vagi intact; or to find out the irritability of the nerve by Dubois's coil, then to poison, and test irritability at different periods, or to paralyze the vagi by atropin or nicotin. I have made use of some of the above methods.

Experiment IV. — Rabbit; vagi cut; artificial respiration; curare.

Time.	Pulse.	Pressure.
	130	154
	Thebain, .0025 gramme.	
A. M. 11 30	135	160
11 30 30	137	176
11 32 30	137	160
11 40	99	138
12 9 45	112	88

Experiment V. — Rabbit; vagi cut; depressor nerve prepared; curare.

Time.	Pulse.	Pressure.
	166	85
	Thebain, .0025 gramme.	
P. M. 1 20	156	76
1 20 30	205	87
	Vagus irritated.	
1 23	158	64
1 26 30	190	70
1 29	Depressor irritated.	
1 29 30	198	40
1 30	Vagus still inhibits.	

Experiment VI. — Rabbit; curare; nicotin; vagi do not respond to moderate currents.

Time.	Pulse.	Pressure.
	148	102
	Thebain, .0025 gramme.	
P. M. 2 40 30	161	108
2 41	161	122
2 41 30	159	116
2 42	155	108
2 49	133	90
3 1	134	90

Experiment VII. — Rabbit; curare; atropin; vagi paralyzed, as tested by strong currents.

Time.	Pulse.	Pressure.
	175	160
	Thebain, .005 gramme.	
P. M. 1 40	186	172
1 40 30	162	176
1 41	153	178
1 54	152	158

It is evident from the above results, when compared with those where the pneumogastrics are intact, that thebain has no action on the cardio-inhibitory ganglia.

ACTION OF THEBAIN ON THE HEART.

To study the action on the heart, I divided the spinal cord between the atlas and the occiput, thus removing the influence of the vaso-motor centre and the accelerator nerves. In addition, the sympathetic, pneumogastric, and depressor nerves were divided. Then the blood-pressure, which depends on the strength and frequency of the heart-beat on the one hand, and on the other on the tonus of the vascular system, was observed.

Experiment VIII. — Rabbit; curare; cardiac nerves in the neck cut; cord cut between the atlas and the occiput (verified by post-mortem examination); bleeding checked by bovista.

Time.	Pulse.	Pressure.
	168	36
	Thebain, .0025 gramme.	
A. M. 11 40	166	36
11 41	174	31
11 41 30	178	34
11 59	108	30

Experiment IX. — Rabbit; curare; cord cut between the atlas and the occiput; hæmorrhage controlled by bovista; all cardiac nerves in the neck cut.

Time.	Pulse.	Pressure.
	133	32
	Thebain, .0025 gramme.	
	137	34
	122	32
	150	30
	140	32
	98	22

The above experiments show that thebain still increases the pulse, but not the pressure. As the main factor in the regulation of the pressure, that is the vaso-motor centre, has been removed in the above experiments, it is to be concluded that thebain has an excitant action on that centre. The increase of pulse must be due to an excitant action on the heart itself, that is, on the excito-motor ganglia, since thebain, as shown above, has no influence on the curve of a striated muscle, and probably, therefore, has little or none on the muscles of the heart.

In this connection it is interesting to notice a difference between the effects of thebain and of strychnia, poisons which in other respects resemble each other closely. Schlesinger[1] has shown that strychnia causes a decided rise of blood-pressure, even after section of the cervical cord, and concludes from this and other experiments that there are vaso-motor centres in the spinal cord. Thebain, unlike strychnia, seems to have no power to cause the blood-pressure to rise.

ACTION OF THEBAIN ON THE VASO-MOTOR CENTRE.

It is well known that the irritation of a sensory nerve causes an excitation of the vaso-motor centre, which is indexed by a rise of pressure. To still further confirm the preceding view that the centre is active, the following experiment was made. Ludwig's gimlet electrodes were screwed into the atlas and the occipital bone for direct irritation.

[1] Wiener medicinische Jahrbücher, 1874, i. 1.

Experiment X. — Rabbit; vagi cut; curare; sciatic nerve prepared.

Time.	Pulse.	Pressure.
	144	150
	Thebain, .005 gramme.	
A. M. 10 40	137	186
10 40 30	143	198
10 41	149	194
10 57 45	130	152 [1]
10 58 15	136	174 [2]
11 1 55	137	188
11 4 15	142	114
	Thebain .005 injected.	
11 4 45	129	124 [3]
11 5 15	130	168

Certainly the vaso-motor centre is in no way paralyzed after the injection of thebain. As indirect irritation always produces a rise of pressure, the sensory nerves and the conductors of their impressions up the cord are not paralyzed. Experiment V. shows that the reflex relation existing between the vaso-motor centre and the depressor nerve is in no way affected.

The following *résumé* will express our results: —

1. Thebain is a tetanoid agent, and pigeons have no special immunity against it.

2. The tetanus is not cerebral, but spinal, in origin.

3. The motor and sensory nerves and the striated muscles are not affected by it.

4. It increases the pulse and blood-pressure by an action on the vaso-motor centre and the heart itself.

5. The reflex action of the depressor nerve is in no way interfered with.

The above experiments were made in the physiological laboratory of Prof. H. P. Bowditch, at the Harvard Medical School. I wish here to express my many obligations to him in their pursuit.

[1] Vaso-motor centre irritated directly.

[2] Vaso-motor centre irritated indirectly, through a sensory nerve, for three seconds.

[3] Vaso-motor centre directly irritated for eleven seconds.